BMJ Open

Manual ventilation to prevent hypoxemia during endotracheal intubation of critically ill adults: protocol and statistical analysis plan for a multi-center randomized trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022139
Article Type:	Protocol
Date Submitted by the Author:	05-Feb-2018
Complete List of Authors:	Casey, Jonathan; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Janz, David; Louisiana State University Health Sciences Center, Russell, Derek ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Vonderhaar, Derek ; Louisiana State University Health Sciences Center, Section of Pulmonary/Critical Care & Allergy/Immunology Joffe, AM; University of Washington, Department of Anesthesiology and Pain Medicine Dischert, Kevin ; University of Washington, Department of Anesthesiology and Pain Medicine Brown, Ryan; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Lester, Michael; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Zouk, Aline ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Gulati, Swati ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Stigler, William ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Rice, TW; Vanderbilt University, Semler, Matthew; Vanderbilt University, Medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adult thoracic medicine < THORACIC MEDICINE

Manual ventilation to prevent hypoxemia during endotracheal intubation of critically ill adults: protocol and statistical analysis plan for a multi-center randomized trial

Jonathan D. Casey, MD[1], David R. Janz, MD, MSc[2], Derek W. Russell, MD[3], Derek J. Vonderhaar, MD[2], Aaron M. Joffe, DO[4], Kevin M. Dischert, MD[4], Ryan M. Brown, MD[1], Michael G. Lester, MD[1], Aline N. Zouk, MD[3], Swati Gulati, MBBS, MS[3], William S. Stigler, MD[3], Todd W. Rice, MD, MSc[1], Matthew W. Semler, MD, MSc[1] for the PreVent Investigators and the Pragmatic Critical Care Research Group.

Affiliations: 1: Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN; 2. Section of Pulmonary/Critical Care & Allergy/Immunology, Louisiana State University School of Medicine, New Orleans, LA; 3. Division of Pulmonary, Allergy, & Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL; 4. Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA

Corresponding author:
Jonathan D. Casey, MD
T-1210 MCN, 1161 21st Ave S., Nashville, TN 37232-2650
Fax: (615) 343-7448
Email: jonathan.d.casey@vanderbilt.edu

Authors contributions: Study concept and design: J.D.C., M.W.S, D.R.J., and T.W.R.; Acquisition of data: J.D.C, D.R.J., D.W.R, D.J.V., A.M.J., K.M.D., R.M.B., M.G.L., A.N.Z, S.G, W.S.S., and M.W.S.; Analysis and interpretation of data: J.D.C, and M.W.S.; Drafting of the manuscript: J.D.C, M.W.S.; Critical revision of the manuscript for important intellectual content: J.D.C, R.M.B., and M.W.S.; Statistical analysis: J.D.C. and M.W.S.; Study supervision: T.W.R.
Sources of Funding: J.D.C. was supported in part by the NIH (2T32HL087738-12). M.W.S. was supported in part by the NHLBI (HL087738-09 and K12HL133117). D.W.R

was supported in part by the NIH/NHLBI (T32HL105346-07). T.W.R. was supported in part by the NIH (R34HL105869). Data collection utilized the Research Electronic Data Capture (REDCap) tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH). The funding institutions had no role in (1) conception, design, or conduct of the study, (2) collection, management, analysis, interpretation, or presentation of the data, or (3) preparation, review, or approval of the manuscript.

Conflicts of Interest: All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declared no potential conflicts of interest with the current work. T.W.R. reported serving on an advisory board for Avisa Pharma, LLC, and as the Director of Medical Affairs for Cumberland Pharmaceuticals, Inc.

Key words for indexing: Endotracheal intubation, ventilation, hypoxemia

Subject Descriptor Number: 4.4 Clinical Trials in Critical Care Medicine

Manuscript Word Count (body only): 4100

Abstract Word Count: 256

Supplemental digital content is available for this article.

ABSTRACT:

Introduction: Hypoxemia is the most common complication during endotracheal intubation of critically ill adults, and it increases the risk of cardiac arrest and death. Manual ventilation between induction and intubation has been hypothesized to decrease the incidence of hypoxemia, but efficacy and safety data are lacking.

Methods and analysis: The Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation (PreVent) trial is a prospective, multi-center, non-blinded randomized clinical trial being conducted in seven intensive care units in the United States. A total of 400 critically ill adults undergoing endotracheal intubation will be randomized 1:1 to receive prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device or no prophylactic ventilation. The primary outcome is the lowest arterial oxygen saturation between induction and two minutes after successful endotracheal intubation, which will be analyzed as an unadjusted, intention-to-treat comparison of patients randomized to prophylactic ventilation versus patients randomized to no prophylactic ventilation. The secondary outcome is the incidence of severe hypoxemia, defined as any arterial oxygen saturation of less than 80% between induction and two minutes after endotracheal intubation. Enrollment began on February 2, 2017 and is expected to be complete in May 2018.

Ethics and dissemination:

The trial was approved by the institutional review boards or designees of all participating centers. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial Registration: The trial was registered with ClinicalTrials.gov (NCT03026322) on January 20, 2017, prior to the enrollment of the first patient on February 2, 2017.

ARTICLE SUMMARY

Strengths and limitations of this study

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes with prophylactic ventilation versus no prophylactic ventilation during endotracheal intubation of critically ill adults
- Enrolling patients at multiple centers using broad inclusion criteria will enhance the generalizability of the findings.
- The nature of the study intervention does not allow blinding
- Despite being one of the largest randomized trials to examine endotracheal intubation of critically ill patients, statistical power will be inadequate to detect differences between study groups in uncommon outcomes (e.g., operator-reported aspiration).

INTRODUCTION

Endotracheal intubation is common in the care of critically ill patients and is frequently associated with complications[1–3]. Hypoxemia occurs in approximately 40% of intubations outside the operating room, and is associated with an increased risk for cardiac arrest and death[2,4–7].

Rapid sequence intubation is the nearly simultaneous administration of a sedative and neuromuscular blocking agent (paralytic) to facilitate endotracheal intubation. This technique is intended to maximize the chances of intubation on the first laryngoscopy attempt and minimize the risk of aspiration. Rapid sequence intubation has been shown to increase the incidence of successful intubation on the first laryngoscopy attempt and to decrease complications compared to intubation without neuromuscular blockade.[8–10] Regardless of the choice of induction agent and neuromuscular blocker, rapid sequence intubation involves an inherent delay between medication administration and onset of paralysis, at which time laryngoscopy is initiated. The relative benefits and risks of providing ventilation to patients during this interval are unknown. Some airway management texts and guidelines recommend that, for patients who are not hypoxemic, no ventilation be provided between induction and intubation, allowing the patient to remain hypopneic or apneic with the onset of sedation and neuromuscular blockade (Figure 1).[11–18] This approach prioritizes minimizing the potential risk of aspiration over any potential benefit of preventing the development of hypoxemia and hypercapnia. Other airway management texts and guidelines recommend the provision of manual ventilation between induction and intubation using a bag-valve-mask device for all patients, including those who are not hypoxemic (referred to hereafter as “prophylactic

ventilation") (Figure 2). [1,17,19–22] This approach prioritizes the potential benefit of preventing the development of hypoxemia and hypercapnia over the potential risk of aspiration. National and international surveys of anesthesiologists demonstrate that up to 50% of anesthesia practitioners report routinely performing prophylactic ventilation between induction and intubation during out-of-OR intubations.[23,24] The most recent published guidelines on intubation of critically ill adults recognizes the arguments for and against prophylactic ventilation without making any recommendation as to whether or not it should be used.[25]

Despite millions of critically ill adults undergoing endotracheal intubation each year, there are currently no high-quality data available to help providers understand the potential benefits and risks of providing prophylactic ventilation between induction and intubation. To address this knowledge gap, we designed a multicenter, randomized trial comparing prophylactic ventilation to no prophylactic ventilation during endotracheal intubation of critically ill adults. We hypothesize that, compared to no prophylactic ventilation, prophylactic ventilation will significantly increase the lowest arterial oxygen saturation between induction and two minutes after endotracheal intubation.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Figure 3; SPIRIT checklist in online supplement, section 1).[26]

Study Design

The Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation (PreVent) trial is a multi-center, parallel-group, un-blinded, pragmatic randomized trial being conducted in seven intensive care units at five medical centers across the United States. The trial compares prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device to no prophylactic ventilation during endotracheal intubation of critically ill adults. Enrollment began on February 2, 2017 and is expected to be complete in May 2018. The primary outcome is lowest arterial oxygen saturation between induction and two minutes after endotracheal intubation. The trial was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center (the coordinating center) with waiver of informed consent (IRB 161962). All participating centers obtained local IRB approval or deferred to Vanderbilt University Medical Center through a central IRB process. The trial was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifiers: NCT03026322). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial.

Study sites

The trial is being conducted at seven academic intensive care units across the United States: a 35-bed medical ICU at Vanderbilt University Medical Center in Nashville, Tennessee; a 38-bed medical, cardiac, and neurological ICU at University Medical Center in New Orleans, Louisiana; a 33-bed medical ICU at Ochsner Medical Center in New Orleans, Louisiana; a 25-bed medical ICU at University of Alabama at Birmingham Medical Center in Birmingham, Alabama; and a 17-bed medical ICU, a 30-bed neurological ICU, and 24-bed trauma ICU at University of Washington Harborview Medical Center in Seattle, Washington.

Population

The trial includes adults (age ≥ 18 years) located in a participating ICU for whom the treating clinicians have determined endotracheal intubation is required, and the planned procedural approach includes administration of an induction agent (with or without neuromuscular blockade) and a first operator who routinely performs endotracheal intubation in the participating ICU. The trial excludes pregnant women, prisoners, and patients for whom the treating clinicians feel the urgency of the intubation precludes safe performance of study procedures or a specific approach to ventilation between induction and intubation is required.

Randomization and Treatment Allocation

Enrolled patients are randomized in a 1:1 ratio to prophylactic ventilation or no prophylactic ventilation. The allocation sequence was generated by study personnel at the coordinating center using computerized randomization in permuted blocks, stratified

by study ICU. Study group assignments were placed in sequentially numbered opaque envelopes and distributed to the study ICUs. Group assignment remains concealed from local study personnel and treating clinicians until the determination has been made that a patient (1) requires endotracheal intubation, (2) meets all inclusion criteria, and (3) meets no exclusion criteria – at which point the enveloped is opened. After enrollment and randomization, patients, treating clinicians, and study personnel at the local site are not blinded to study group assignment.

Study Interventions

Definitions

Ventilation between induction and endotracheal intubation refers to the delivery of positive pressure breaths using a non-invasive ventilator or a bag-valve-mask device. Prophylactic ventilation describes ventilation administered to a patient without hypoxemia to prevent the development of hypoxemia. Separately, ventilation may represent treatment of hypoxemia for patients who are experiencing hypoxemia at the initiation of ventilation. The focus of this trial is on the administration of manual ventilation with a bag-valve-mask device to prevent the development of hypoxemia. Treatment of hypoxemia with manual ventilation is not considered prophylactic ventilation and is allowed at any time in either study group. Administration of ventilation with a non-invasive ventilator between induction and laryngoscopy is prohibited in both study groups because it represents a source of confounding with regard to the provision of prophylactic ventilation. Pre-oxygenation prior to induction is allowed in either group with any pre-oxygenation modality, including non-invasive ventilation.

Prophylactic Ventilation

For patients assigned to the prophylactic ventilation group, manual ventilation is provided using a bag-valve-mask device beginning at induction and continuing until the initiation of laryngoscopy. If more than one attempt at laryngoscopy occurs, manual ventilation using a bag-valve-mask device may be reinstituted between laryngoscopy attempts. Manual ventilation may be discontinued at any point if felt by the treating clinicians to be necessary for patient safety.

Manual ventilation with a bag-valve-mask device is a routinely employed technique familiar to clinicians who perform endotracheal intubation in the ICU. In keeping with the pragmatic nature of the trial, manual ventilation with a bag-valve-mask device is provided during the trial by the same treating clinicians who would perform the intervention outside of a research setting. Trainees responsible for airway management in participating units received an educational intervention prior to the beginning of enrollment reviewing best practices in manual ventilation using a bag-valve-mask device. This training emphasized proper mask placement, airway patency maneuvers, positive end-expiratory pressure (PEEP), oxygen flow rates, and ideal ventilation rates and volumes. In addition, the group assignment sheet for the prophylactic ventilation group includes reminders of best practices for manual ventilation using a bag-valve-mask device, including instructions to use: oxygen flow rates of at least 15 liters per minute; a PEEP valve set to 5-10 cm of water; an oral airway; a 2-handed mask seal performed by the intubating clinician with a head-tilt-chin-lift (with a stock photograph demonstrating proper technique); and ventilation at 10 breaths per minute until

laryngoscopy. Details of patients' receipt of manual ventilation between induction and intubation are prospectively recorded. Failure to administer manual ventilation with a bag-valve-mask device beginning at induction is documented as a protocol violation.

No Prophylactic Ventilation

Patients assigned to the no prophylactic ventilation group do not receive prophylactic ventilation between induction and intubation. Manual ventilation is allowed as treatment (1) for hypoxemia (oxygen saturation < 90%) or (2) following a failed laryngoscopy attempt. In addition, manual ventilation may be initiated at any point if felt by the treating clinicians to be necessary for the safe treatment of the patient. Details of patients' receipt of ventilation between induction and endotracheal intubation are prospectively recorded. Administration of ventilation using a bag-valve-mask device before the first attempt at laryngoscopy in a patient who does not experience hypoxemia (oxygen saturation < 90%) is documented as a protocol violation.

Co-interventions

Study group assignment determines only the approach to prophylactic ventilation between induction and endotracheal intubation. Treating clinicians determine the need for intubation, approach to pre-oxygenation, patient positioning, choice and timing of medications for induction and neuromuscular blockade, choice of laryngoscope type and size, use of cricoid pressure, and use of additional airway management equipment.

Data Collection

A trained, independent observer, not affiliated with the performance of the procedure collects data for key peri-procedural outcomes, including oxygen saturation and systolic blood pressure at induction, lowest arterial oxygen saturation and systolic blood pressure between induction and 2 minutes following intubation, vasopressor administration, and time to intubation. The accuracy of data collection by the independent observers is confirmed by concurrent assessment of the same outcomes by the primary investigators for a convenience sample of approximately 10% of study intubations.

Cormack-Lehane grade of glottic view,[27] subjective difficulty of intubation, and airway complications during the procedure are reported by the operator. Operators self-report their prior intubating experience at the time of each study intubation.

Study personnel collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes from the medical record. The following variables are collected:

Baseline: Age, gender, height, weight, body mass index, race, Acute Physiology and Chronic Health Evaluation (APACHE II score), active medical problems at the time of intubation, active comorbidities complicating intubation, comorbidities known to increase risk of aspiration (history of gastroesophageal reflux, narcotic use, functional or mechanical gastrointestinal obstruction, previous esophageal surgery, head injury, active emesis, or active upper gastrointestinal bleeding), indication for intubation, reintubation status, preoxygenation technique, operator experience, non-invasive ventilator use, vasopressor use, arterial blood gas results, and the highest fraction of inspired oxygen delivered (FiO2), lowest

systolic blood pressure observed, and lowest oxygen saturation observed in the six hours preceding intubation.

Peri-procedural: Pre-procedural fluid and vasopressors. Date and time of sedative administration, saturation at time of sedative administration, type and dose of sedative, type and dose of neuromuscular blocker, use of manual ventilation starting at the time of induction, any use of ventilation during the intubation, indication for ventilation (study assignment, oxygen saturation less than 90%, following a failed attempt, other), use of oral or nasal airway, use of cricoid pressure, laryngoscope type and size, total number of attempts, airway grade, airway difficulty, use of rescue device(s), need for additional operators, date and time of first laryngoscopy attempt, date and time of successful intubation, mechanical complications (esophageal intubation, airway trauma), bradycardia, and the presence of aspiration between induction and intubation (reported by operator).

0-48 hours: All chest imaging obtained within the first 48 hours after intubation, post intubation shock or cardiac arrest, Highest and lowest SaO2, FiO2, PEEP, and systolic blood pressure in the 1, 6, and 24 hours after intubation.

In-Hospital Outcomes: Ventilator-free days, ICU-free days, and in-hospital mortality. Definitions for Ventilator-free days and ICU-free days can be found in the online supplement, sections 2 and 3.

Primary Outcome

The primary outcome is the lowest arterial oxygen saturation measured by continuous pulse oximetry (SpO2) between induction and 2 minutes after endotracheal intubation ("lowest arterial oxygen saturation") as documented by the independent observer.

Secondary Outcome

The single, pre-specified, secondary outcome is the incidence of severe hypoxemia, defined as any oxygen saturation less than 80% between induction and 2 minutes after endotracheal intubation. The optimal outcome for clinical trials attempting to improve oxygenation during endotracheal intubation of critically ill adults is unknown. In addition to the primary outcome of lowest arterial oxygen saturation as a continuous variable, some experts have recommended examination of the endpoint of "severe hypoxemia" as a dichotomous outcome. We therefore highlight the incidence of oxygen saturation less than 80% as our pre-specified approach to analysis of lowest oxygen saturation as a dichotomous outcome. All additional outcomes are exploratory and will be considered hypothesis generating.

Main Safety Outcomes

The main safety outcomes will be the lowest SpO2, highest FiO2, and highest PEEP in the time period of 6 to 24 hours post-intubation. The outcomes of SpO2, FiO2, and PEEP are selected to capture objective clinical manifestations of peri-procedural aspiration. The time point of 6 to 24 hours post-intubation is chosen to account for the practice, at some centers, of initiating patients at 100% FiO2 and low PEEP immediately

after intubation, and subsequently titrating FiO2 and PEEP over several hours to achieve the target SpO2.

Exploratory Procedural Outcomes

- Cormack-Lehane grade of glottic view
- Operator-assessed difficulty of intubation
- Incidence of successful intubation on the first laryngoscopy attempt
- Number of laryngoscopy attempts
- Time from induction to successful intubation
- Incidence of esophageal intubation
- Need for additional airway equipment or a second operator
- Incidence of lowest oxygen saturation less than 90%
- Change in oxygen saturation from induction to lowest oxygen saturation
- Incidence of desaturation, defined as a change in oxygen saturation of more than 3% from induction to 2 minutes after endotracheal intubation

Exploratory Safety Outcomes

- Operator-reported aspiration during the procedure, defined as visualization of oropharyngeal or gastric contents in the pharynx, larynx, or trachea between induction and completion of airway management
- New infiltrate on chest x-ray in the 48 hours following intubation, as determined by an independent reviewer; details in online supplement, section 4

- New pneumothorax within 24 hours of intubation, as determined by an independent reviewer; details in online supplement, section 4
- New pneumomediastinum within 24 hours of intubation, as determined by an independent reviewer; details in online supplement, section 4
- Lowest systolic blood between induction and two minutes after endotracheal intubation
- New systolic blood pressure < 65 mmHg or new vasopressor administration between induction and 2 minutes after endotracheal intubation
- Cardiac arrest within one hour of intubation
- Death within one hour of intubation
- Lowest SpO2, highest FiO2, and highest PEEP from 0-1 and 1-6
- The composite of operator-reported pulmonary aspiration, new chest x-ray infiltrate, OR lowest oxygen saturation < 80% between induction and completion of endotracheal intubation

Exploratory Clinical Outcomes

- Ventilator-free days to 28 days
- ICU-free days to 28 days
- In-hospital mortality

Sample Size Estimation

Full details of the initial sample size calculation can be found in the online supplement, section 5. In short, assuming a standard deviation of 14% in lowest oxygen saturation (the primary outcome) and less than 5% missing data, we calculated that enrolling 350 patients would provide 90% power to detect a difference of 5% between groups in lowest oxygen saturation at a two-sided alpha of 0.05. The trial protocol and DSMB charter specified that the DSMB would recommend sample size re-estimation at the interim analysis if the standard deviation for lowest oxygen saturation in the control arm was larger than 14%, in order to prevent the final study from being underpowered to detect the planned difference between groups in lowest oxygen saturation. At the interim analysis, the observed standard deviation for lowest oxygen saturation in the control arm was 15%. To maintain 90% statistical power to detect a 5% difference between groups in lowest oxygen saturation, the DMSB recommended increasing the sample size to 400 patients. Additional details of the sample size re-estimation can be found in the online supplement, section 6.

Data and Safety Monitoring Board and Interim Analysis

An independent DSMB was appointed to oversee the conduct of the trial and review one interim analysis (DSMB charter available in the online supplement, section 7). The DSMB was comprised of two academic intensivists experienced in the conduct of clinical trials. The DSMB conducted a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 175 patients. The stopping boundary for efficacy was specified as a P value of 0.001 or less for the difference between groups in the primary outcome. Use of a conservative Haybittle-Peto

boundary (P < 0.001) allows the final analysis to be performed using an unchanged level of significance (P = 0.05). The primary determination of safety was based on the highest FiO2 and highest PEEP between 6 and 24 hours after intubation. If (1) the P value for the difference between study groups in both of these physiologic variables was less than 0.001, (2) the difference between groups in both physiologic variables was concordant in direction with the point estimate for in-hospital mortality, and (3) the P value for the difference between study groups in in-hospital mortality was less than 0.1, it was recommended that the study be stopped early for safety.

The DSMB was also provided with data in each group on the rates of operator-reported aspiration and new infiltrates, pneumothorax, or pneumomediastinum on chest imaging. Although no pre-specified rules dictated stopping based on operator-reported aspiration or imaging findings without associated changes in physiologic or clinical outcomes, the DSMB reserved the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

At the time of submission of this manuscript, the DSMB has completed the sole planned interim analysis following the enrollment of the first 175 patients. The DSMB has recommended continuing the trial to completion with the only change being to increase the sample size to 400 patients, as described above.

Additional details on data storage, patient privacy, and the pre-specified process for protocol changes can be found in the online supplement, sections 8 and 9.

Statistical Analysis Principles

All analyses will be performed using Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and confirmed with SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) or R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank-sum test for continuous variables, and the chi-square test or Fishers exact test for categorical variables. Agreement between continuous variables measured independently by two observers will be examined using Spearman rank correlation coefficient and Bland-Altman analysis. A two-sided P value < 0.05 will indicate statistical significance.

Primary Analysis

The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to prophylactic ventilation versus patients randomized to no prophylactic ventilation with regard to the primary outcome of lowest arterial oxygen saturation between induction and 2 minutes after endotracheal intubation. The difference between the two study groups will be compared using the Mann-Whitney rank-sum test.

Secondary Analyses

We will conduct the following pre-specified secondary analyses:

1. **Secondary and Exploratory Outcomes**. We will perform unadjusted, intention-to-treat analyses comparing patients in the prophylactic ventilation group to the no prophylactic ventilation group with regard to each of the pre-specified secondary and exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney rank-sum test and categorical variables with the chi-square test.
2. **Per-Protocol Analysis**. We will perform a per-protocol analysis comparing patients who received prophylactic manual ventilation beginning at induction (regardless of group assignment) to patients who did not receive prophylactic manual ventilation beginning at induction (regardless of group assignment). Patients who were hypoxemic at induction and received manual ventilation as treatment for hypoxemia will be analyzed in the group to which they were assigned.
3. **Effect Modification (Subgroup Analyses)**. We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect modification by fitting a linear regression model for the primary outcome of lowest arterial oxygen saturation. Independent variables will include study group assignment, the potential effect modifier variable of interest, and the interaction between the two (e.g., study group*oxygen saturation at induction). Significance will be determined by the *P* value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups

derived from categorical variables will be displayed as a forest plot. Continuous variables will be analyzed using restricted cubic splines with 3-5 knots and preferentially displayed as continuous variables using a locally weighted regression or partial effects plots. If the presentation of data requires it, dichotomization of continuous variables for inclusion in a forest plot will be performed. Pre-specified subgroups that may modify the effect of prophylactic ventilation include:

1. Predicted lowest arterial oxygen saturation ("risk of hypoxemia") as calculated by a pre-specified multivariable model (continuous variable)
2. Oxygen saturation at induction (continuous variable)
3. Highest FiO2 received in the 6 hours prior to intubation (continuous variable)
4. Receipt of non-invasive ventilation in the 6 hours prior to intubation (yes / no)
5. Indication for intubation (hypoxemic respiratory failure, not hypoxemic respiratory failure)
6. Neuromuscular blocking agent (depolarizing, non-depolarizing, none)
7. APACHE II score at enrollment (continuous variable)
8. Body mass index (continuous variable)
9. Operator's prior number of endotracheal intubations (continuous variable)

10. Operator training (pulmonary/critical care medicine, anesthesia)
11. Type of laryngoscope (direct laryngoscope, video laryngoscope)

4. **Multivariable Modeling to Account for Confounding**. To account for relevant confounders, we will develop a linear regression model with the primary outcome as the dependent variable and study group and relevant confounders included as independent variables (age, APACHE II score at enrollment, oxygen saturation at induction, highest FiO2 delivered in the 6 hours prior to intubation, and receipt of non-invasive ventilation in the 6 hours prior to intubation)

Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed. As sensitivity analyses, the primary analysis will be repeated with missing data imputed by (1) assigning a value of "0" to data missing for the lowest arterial oxygen saturation in the prophylactic ventilation group and "100" to data missing for the lowest arterial oxygen saturation in the no prophylactic ventilation group, and (2) assigning a value of "100" to data missing for the lowest arterial oxygen saturation in the prophylactic ventilation group and a value of "0" to data missing from the no prophylactic ventilation group.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. All additional analyses will be considered hypothesis generating, and no corrections for multiple comparisons will be performed.

Trial Status

PreVent is an ongoing pragmatic trial comparing prophylactic ventilation using a bag-valve-mask to no prophylactic ventilation during endotracheal intubation of critically ill adults. Patient enrollment began on February 2, 2017, and we estimate that enrollment will end in May 2018.

Ethics and dissemination:

Consent

Prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device and no prophylactic ventilation are each recommended approaches to endotracheal intubation of acutely ill adults.[13,25] Currently, no randomized trials or evidence-based guidelines support the choice of one approach over the other. Both approaches are used intermittently in current care in the study ICUs. Moreover, the current study specifically excludes patients for whom treating clinicians feel that the provision of prophylactic ventilation is either required or contraindicated.

The current study is felt by the investigators to represent minimal risk because the interventions studied (1) are used in current clinical care in the participating ICUs, (2) are interventions to which patients would be exposed even if not participating in

research, (3) have no prior data to suggest the superiority of one approach over the other, and (4) are equivalent options from the perspective of the treating clinicians performing the procedure (otherwise the patient is excluded from the trial). Additionally, endotracheal intubation of critically ill adults is frequently a time-sensitive procedure for which obtaining informed consent is impractical. Given the minimal risk and impracticability of obtaining informed consent, a waiver of informed consent was requested from the Vanderbilt University Institutional Review Board.

The results of the trial will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

CONCLUSION

We describe, before the conclusion of enrollment or data un-blinding, our approach to analyzing the data from a pragmatic multicenter randomized trial comparing prophylactic ventilation between induction and intubation using a bag-valve-mask to no prophylactic ventilation (PreVent trial). We anticipate that this pre-specified framework will enhance the utility of the reported result and allow readers to better judge the impact.

REFERENCES

1 Schwartz DE, Matthay MA, Cohen NH. Death and Other Complications of Emergency Airway Management in Critically Ill Adults A Prospective Investigation of 297 Tracheal Intubations. *J Am Soc Anesthesiol* 1995;**82**:367–76.

2 Simpson GD, Ross MJ, McKeown DW, *et al.* Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;**108**:792–9. doi:10.1093/bja/aer504

3 Leibowitz AB. Tracheal intubation in the intensive care unit: Extremely hazardous even in the best of hands*: *Crit Care Med* 2006;**34**:2497–8. doi:10.1097/01.CCM.0000235993.47514.8F

4 Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: A justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth* 2004;**16**:508–16. doi:10.1016/j.jclinane.2004.01.007

5 Martin LD, Mhyre JM, Shanks AM, *et al.* 3,423 Emergency Tracheal Intubations at a University Hospital: Airway Outcomes and Complications. *Anesthesiology* 2011;**114**:42–8. doi:10.1097/ALN.0b013e318201c415

6 Griesdale DEG, Bosma TL, Kurth T, *et al.* Complications of endotracheal intubation in the critically ill. *Intensive Care Med* 2008;**34**:1835–42. doi:10.1007/s00134-008-1205-6

7 Semler MW, Janz DR, Lentz RJ, *et al.* Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med* 2015;**193**:273–80. doi:10.1164/rccm.201507-1294OC

8 Brown III CA, Bair AE, Pallin DJ, *et al.* Techniques, Success, and Adverse Events of Emergency Department Adult Intubations. *Ann Emerg Med* 2015;**65**:363–370.e1. doi:10.1016/j.annemergmed.2014.10.036

9 Li J, Murphy-Lavoie H, Bugas C, *et al.* Complications of emergency intubation with and without paralysis. *Am J Emerg Med* 1999;**17**:141–3. doi:10.1016/S0735-6757(99)90046-3

10 Jaber S, Amraoui J, Lefrant J-Y, *et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: A prospective, multiple-center study*: *Crit Care Med* 2006;**34**:2355–61. doi:10.1097/01.CCM.0000233879.58720.87

11 Wylie WD. The Use of Muscle Relaxants at the Induction of Anaesthesia of Patients with a Full Stomach. *Br J Anaesth* 1963;**35**:168–73. doi:10.1093/bja/35.3.168

12 Salem MR. Anesthetic management of patients with “a full stomach”. A critical review. *Anesth Analg* 1970;**49**:47–55.

13 Walls RM. Rapid Sequence Intubation. In: *Manual of Emergency Airway Management*. Philadelphia: : Lippincott Williams & Wilkins, a Wolters Kluwer business 2012. 221–31.

14 Natanson C, Shelhamer JH, Parrillo JE. Intubation of the Trachea in the Critical Care Setting. *JAMA* 1985;**253**:1160–5. doi:10.1001/jama.1985.03350320084023

15 Caputo N, Azan B, Domingues R, *et al.* Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial). *Acad Emerg Med* 2017;**24**:1387–94. doi:10.1111/acem.13274

16 Stollings JL, Diedrich DA, Oyen LJ, *et al.* Rapid-Sequence Intubation: A Review of the Process and Considerations When Choosing Medications. *Ann Pharmacother* 2014;**48**:62–76. doi:10.1177/1060028013510488

17 El-Orbany M, Connolly LA. Rapid sequence induction and intubation: current controversy. *Anesth Analg* 2010;**110**:1318–25. doi:10.1213/ANE.0b013e3181d5ae47

18 Stept WJ, Safar P. Rapid induction-intubation for prevention of gastric-content aspiration. *Anesth Analg* 1970;**49**:633–6.

19 Nagelhout JJ. AANA journal course. Update for nurse anesthetists. Aspiration prophylaxis: is it time for changes in our practice? *AANA J* 2003;**71**:299–303.

20 Herriger A, Frascarolo P, Spahn DR, *et al.* The effect of positive airway pressure during pre-oxygenation and induction of anaesthesia upon duration of non-hypoxic apnoea. *Anaesthesia* 2004;**59**:243–7. doi:10.1111/j.1365-2044.2004.03615.x

21 Frerk C, Mitchell VS, McNarry AF, *et al.* Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *BJA Br J Anaesth* 2015;**115**:827–48. doi:10.1093/bja/aev371

22 Myatra SN, Ahmed SM, Kundra P, *et al.* The All India Difficult Airway Association 2016 guidelines for tracheal intubation in the Intensive Care Unit. *Indian J Anaesth* 2016;**60**:922–30. doi:10.4103/0019-5049.195485

23 Ehrenfeld JM, Cassedy EA, Forbes VE, *et al.* Modified Rapid Sequence Induction and Intubation: A Survey of United States Current Practice. *Anesth Analg* 2012;**115**:95–101. doi:10.1213/ANE.0b013e31822dac35

24 Schlesinger S, Blanchfield D. Modified rapid-sequence induction of anesthesia: a survey of current clinical practice. *AANA J* 2001;**69**:291–8.

25 Higgs A, McGrath BA, Goddard C, *et al.* Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* doi:10.1016/j.bja.2017.10.021

26 SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/23303884 (accessed 8 Jan 2018).

27 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;**39**:1105–11. doi:10.1111/j.1365-2044.1984.tb08932.x

FIGURES

Figure 1.

Phases of rapid sequence intubation without prophylactic manual ventilation.
“NMB” is Neuromuscular blockade. “RSI” is rapid sequence intubation

Figure 2.

Phases of rapid sequence intubation with prophylactic manual ventilation.
“NMB” is Neuromuscular blockade. “RSI” is rapid sequence intubation

Figure 3.

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments.
Baseline variables obtained from electronic medical record include: demographic characteristics, indication for intubation, history of pulmonary disease, severity of illness at enrollment, risk factors for aspiration, non-invasive ventilator use, and highest FIO2 in the 6 hours prior to intubation. Peri-procedural variables, including oxygen saturation at induction, lowest arterial oxygen saturation between induction and 2 minutes following endotracheal intubation, and time to intubation will be collected by a trained, independent observer, not affiliated with the performance of the procedure. Clinical outcomes include: vital status, number of ventilator-free days to 28 days, and number of ICU-free days to 28 days. ICU is intensive care unit; ETI is endotracheal intubation.

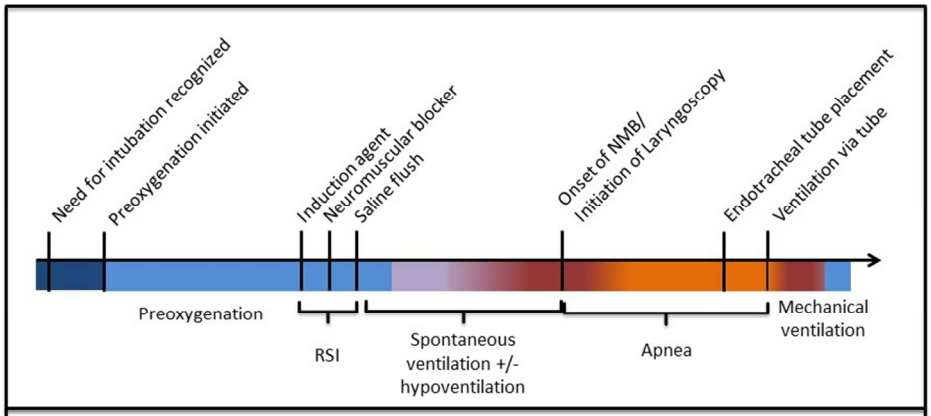

Figure 1: Phases of "Classic" Rapid Sequence Intubation

Figure 1

254x190mm (96 x 96 DPI)

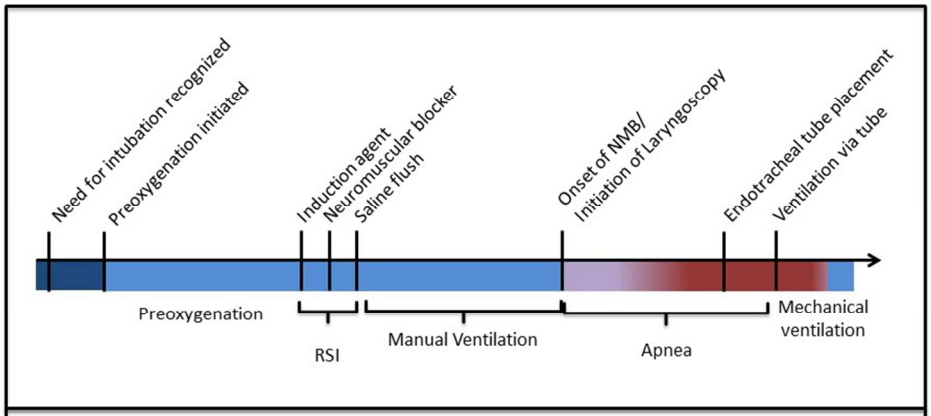

Figure 2: Phases of Modified Rapid Sequence Intubation

Figure 2

254x190mm (96 x 96 DPI)

ONLINE SUPPLEMENT TO:

Preventing hypoxemia with manual ventilation during endotracheal intubation: protocol and statistical analysis plan for a multi-center randomized trial

Jonathan D. Casey, David R. Janz, MD, Derek W. Russell, Derek J. Vonderhaar, Aaron M. Joffe, Kevin M. Dischert, Ryan M. Brown, Michael G. Lester, Aline N. Zouk, Swati Gulati, William S. Stigler, Todd W. Rice, Matthew W. Semler for the PreVent Investigators and the Pragmatic Critical Care Research Group.

Table of Contents

1. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1-2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1-2

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-2, 8, 18-19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-23
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-23
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20-23

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19, S10-S17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19, S10-S17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	S13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	S13-S14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24-25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	S9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	24-25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	S9

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1-2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	1-2, 23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	S9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

2. Definition of Ventilator Free Days (VFDs)

Ventilator-free days are defined as the number of days on which the patient is alive and breathing without assistance between the patient's final receipt of assisted breathing within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

3. Definition of ICU-Free Days (ICUFDs)

ICU-free days are defined as the number of days on which the patient is alive and not in an ICU between the patient's final transfer out of the ICU within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, ICU-free days are 0. If a patient is in an ICU at day 28, ICU-free days are 0. Otherwise, ICU-free days are calculated as 28 minus the study day on which the patient was ultimately transferred out of the ICU. All data will be censored at the time of first hospital discharge or 28 days.

4. Adjudication of new infiltrate, pneumothorax, or pneumomediastinum

Exploratory safety outcomes include new infiltrate on chest x-ray in the 48 hours following intubation, new pneumothorax within 24 hours of intubation, and new pneumomediastinum within 24 hours of intubation. The presence of new infiltrate, new pneumothorax, or new pneumomediastinum are determined by independent review of chest imaging by two pulmonary and critical care medicine attending physicians at the coordinating center who are unaware of study group assignment. Each site provides the coordinating center the most recent chest x-ray prior to intubation and all chest x-rays obtained between intubation and 48 hours after intubation. Each film is de-identified and reviewed independently by two pulmonary and critical care medicine attending physicians who are unaware of study group assignment. The presence or absence of new infiltrate, new pneumothorax, or new pneumomediastinum is recorded using a standardized data collection sheet. If a pre-intubation chest x-ray is not available, any infiltrate, pneumothorax, or pneumomediastinum is considered to be new. Any assessments that are discordant between the two independent reviewers are resolved by independent, blinded review by a third pulmonary and critical care medicine physician.

5. Initial Sample Size Calculation

The initial sample size calculation was made using data from previous prospective trials enrolling a similar population of patients in similar ICUs. These trials demonstrated a standard deviation of 14% in the primary outcome of lowest arterial oxygen saturation.[1] The difference between groups in lowest arterial oxygen saturation felt to be clinically meaningful in prior trials was 5%.[2–4] Using nQuery Advisor® version 7.0 with the above assumptions and a two-sided alpha level of 0.05, we calculated that achieving a statistical power of 90% would require enrollment of 332 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 350 patients was planned.

6. Sample Size Re-estimation

The trial protocol and DSMB charter specified that the DSMB would recommend sample size re-estimation at the interim analysis if the standard deviation for lowest oxygen saturation in the control arm was larger than 14%, in order to prevent the final study from being underpowered to detect the planned difference between groups in lowest oxygen saturation. At the interim analysis, the observed standard deviation for lowest oxygen saturation in the control arm was 15%. Using nQuery Advisor® version 7.0, we calculated that maintaining a statistical power of 90% to show a difference of 5% in lowest oxygen saturation with a standard deviation of 15% and a two-sided alpha level of 0.05 would require enrollment of 380 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 400 patients would be required. Based on these calculations, the DMSB recommended increasing the final planned sample size to 400 patients.

To understand the ability of the updated sample size to inform the assessment of the safety of the intervention, we conducted exploratory sample size calculations for the safety outcomes. The main safety outcomes are lowest oxygen saturation, highest fraction of inspired oxygen (FiO2), and highest positive end-expiratory pressure (PEEP) from 6 to 24 hours after intubation between the two study groups. In the 24 hours following intubation in a prior trial in a similar population, the standard deviation in lowest oxygen saturation was 11%, the standard deviation in highest FiO2 was 0.33, and the standard deviation in highest PEEP was 3.3 cmH_2O.[28] By enrolling 400 patients, we estimated that we would have 80% statistical power at an alpha of 0.05 to detect a 3.1% difference between groups in the lowest oxygen saturation in the 24

hours after intubation, a 0.09 difference in the highest FiO2, and a 0.9 cmH_2O difference in highest PEEP.

The exploratory safety outcomes are less common clinical events than the primary outcome and the main safety outcomes. Operator-reported aspiration has occurred in prior trials at an incidence of 1.0-6.0%. Therefore, enrollment of 400 patients would provide 80% statistical power at an alpha level of 0.05 to detect an absolute difference in the incidence of aspiration between groups of 6.0-10.5%. New infiltrate on chest imaging following intubation has been reported in prior studies to occur with an incidence of 4-8%.[1,29] Enrollment of 400 patients would provide 80% power at an alpha level of 0.05 to detect an absolute difference between groups of 8.1-9.9%, respectively.

7. Data and Safety Monitoring Board Charter

DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for

"Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial"

Jonathan D. Casey, MD

David R. Janz, MD, MSc

Todd W. Rice, MD, MSc

Matthew W. Semler MD, MSc

Confidential Information

The information contained within this Charter is confidential and intended for the use of the DSMB

_____

DSMB Member Printed Name

_____ _____

DSMB Member Signature Date

Charter, Data and Safety Monitoring Board for

Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

January 2017

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the sponsor of this trial, Matthew W Semler, MD, MSc and is required to provide recommendations about starting, continuing, and stopping the trial. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Performance of individual centers
- Participant safety
- Notification of and referral for adverse events

3. Organization and Interactions

Communication with DSMB members will be primarily through Dr. Semler. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A. The DSMB consists of two physicians experienced in critical care, the conduct of clinical trials including data and safety monitoring, and have formal training to conduct statistical analyses necessary for the planned interim analysis. Dr. Semler or his designee will serve as the Executive Secretary (ES) and be responsible for keeping the minutes of the open sessions. The Chair of the DSMB will be responsible for recording the minutes of the closed sessions and for the timely transmission of the final DSMB recommendations to Dr. Semler. Dr. Semler will be responsible for the timely notification of investigators of all DSMB recommendations.

5. Scheduling, Timing, Content, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter and the study protocol, including the Data Safety Monitoring Plan. Dr. Semler or his designee can conduct this meeting with individual DSMB members or as a group. Enrollment in the study cannot begin until Dr. Semler has accepted the DSMB's recommendation for approval and IRB approval has been obtained. All DSMB members must sign and return the charter to Dr. Semler or his designee to indicate their approval.

Conference calls are to be held approximately twice a year, with additional conference calls scheduled as needed. Conference calls will be scheduled by Dr. Semler or the ES in collaboration with the DSMB members.

The DSMB will review 30-day data after 175 subjects have been enrolled; enrollment will continue during DSMB review. The primary focus of this review will be efficacy and safety. All data will be supplied to the DSMB with blinded treatment groups; however, the DSMB will be able to request unblinding for any reason. All serious adverse events thought to be related to study procedures will be reported to the DSMB on an ongoing basis; the study will be stopped for a safety evaluation by the DSMB if they have any concerns based on either the interim data analysis or review of serious adverse events.

The agenda for DSMB meetings and calls will be drafted by Dr. Semler. Dr. Semler will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the ES two weeks before each call.

Before each teleconference the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last call. If a new conflict is reported, the Chair will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

It is expected that all DSMB members will attend every call and respond to electronic mail communications promptly. A quorum of this DSMB will be all two members.

6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, Dr. Semler will present information to the DSMB on behalf of the study investigators with time for discussion.

- During the **closed sessions**, the DSMB will discuss confidential and/or unblinded data from the study. Steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

- Initial summary: The ES is responsible for assuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations. Dr. Semler will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, Dr. Semler will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The ES is responsible for the accuracy and transmission of the formal DSMB minutes within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email.

8. Reports to the DSMB

For each meeting, Dr. Semler will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first meeting what data they wish to review and how it should be presented. Data requests can be modified at subsequent meetings.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the clinical endpoints and safety monitoring plans. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial.

10. Stopping Rules

At the meeting for the planned interim analysis (at least 30 days after enrollment of 175 patients), the DSMB will be provided the following blinded data in raw format:

1. Study group assignment of each patient (A vs B)
2. Lowest arterial oxygen saturation during the procedure
3. Lowest arterial oxygen saturation in the 24 hours following intubation
4. Highest fraction of inspired oxygen in the 24 hours following intubation

5. Highest positive end expiratory pressure in the 24 hours following intubation
6. Mortality
7. Ventilator-free days

At this interim analysis, the DSMB will be asked to perform 2 analyses using these data: a efficacy analysis and safety analysis as described below. At the completion of these analyses, the DSMB will notify Dr. Semler if the trial should be stopped for any of these three reasons or continued to completion. The DSMB will not make Dr. Semler or any of the investigators aware of the results of any of their analyses. At the interim analysis or at any other time where the DSMB is deciding if the trial should be stopped or continued, all of the members of the DSMB must agree that the trial should be stopped or continued.

11. Efficacy Stopping Rules

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, 30 days after enrollment of 175 patients. Enrollment will continue during this period. The **stopping boundary for efficacy** will be met if the *P* value for the difference between groups in the primary outcome is 0.001 or less. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of both interventions as a part of usual care, there will be **no stopping boundary for futility**.

12.Safety Stopping Rule

With regards to safety, the DSMB will be able to stop study accrual at any time if there is concern for safety. Other than these concerns, the DSMB will be asked to formally evaluate the safety of the trial at the interim analysis described above 30 days after enrollment of 175 patients. The primary determination of safety will be based on the highest fraction of inspired oxygen and highest positive end-expiratory pressure between 6 and 24 hours after intubation. The **safety stopping boundary** is as follows:

1. The *P* value for the difference between study groups in both of these physiologic variables is < 0.001, AND
2. The difference between groups in both physiologic variables is concordant in direction with the point estimate for in-hospital mortality, AND
3. The *P* value for the difference between study groups in in-hospital mortality is < 0.1

The DSMB will also be provided with blinded data on all outcomes collected by the trial to use in their review of trial safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, unblind the study assignments, or request modifications of the study protocol as required to protect patient safety. Finally, the DSMB will have the ability to monitor the standard deviation of the primary outcome in the

control group at the interim analysis and can ask that the study be re-powered if the standard deviation of the primary outcome is different from our original estimate of 14%. This standard deviation will be calculated by the investigators and given to the DSMB in a blinded fashion.

8. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

9. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

Figure 3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments.

	STUDY PERIOD						
	Enrolment	Allocation	On-Study				Follow Up
TIMEPOINT	Decision to perform ETI	Prior to Induction	Induction & NMB	ETI	2 min post-ETI	48 hrs post-ETI	Discharge or 30 days after enrollment
ENROLMENT:	X						
Eligibility screen	X						
Allocation		X					
INTERVENTIONS:							
Prophylactic Ventilation			⟷				
Screening for contraindications	X	X	X	X			
No Prophylactic Ventilation			⟷				
Screening for contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-procedural variables		X	X	X	X		
Clinical Outcomes						X	X

215x279mm (200 x 200 DPI)

BMJ Open

Manual ventilation to prevent hypoxemia during endotracheal intubation of critically ill adults: protocol and statistical analysis plan for a multi-center randomized trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022139.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jun-2018
Complete List of Authors:	Casey, Jonathan; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Janz, David; Louisiana State University Health Sciences Center, Russell, Derek ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Vonderhaar, Derek ; Louisiana State University Health Sciences Center, Section of Pulmonary/Critical Care & Allergy/Immunology Joffe, AM; University of Washington, Department of Anesthesiology and Pain Medicine Dischert, Kevin ; University of Washington, Department of Anesthesiology and Pain Medicine Brown, Ryan; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Lester, Michael; Vanderbilt University Medical Center, Division of Allergy, Pulmonary, and Critical Care Medicine Zouk, Aline ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Gulati, Swati ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Stigler, William ; University of Alabama at Birmingham, Division of Pulmonary, Allergy, & Critical Care Medicine Rice, TW; Vanderbilt University, Semler, Matthew; Vanderbilt University, Medicine
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Emergency medicine, Respiratory medicine
Keywords:	Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adult thoracic medicine < THORACIC MEDICINE

Manual ventilation to prevent hypoxemia during endotracheal intubation of critically ill adults: protocol and statistical analysis plan for a multi-center randomized trial

Jonathan D. Casey, MD[1], David R. Janz, MD, MSc[2], Derek W. Russell, MD[3], Derek J. Vonderhaar, MD[2], Aaron M. Joffe, DO[4], Kevin M. Dischert, MD[4], Ryan M. Brown, MD[1], Michael G. Lester, MD[1], Aline N. Zouk, MD[3], Swati Gulati, MBBS, MS[3], William S. Stigler, MD[3], Todd W. Rice, MD, MSc[1], Matthew W. Semler, MD, MSc[1] for the PreVent Investigators and the Pragmatic Critical Care Research Group.

Affiliations: 1: Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN; 2. Section of Pulmonary/Critical Care & Allergy/Immunology, Louisiana State University School of Medicine, New Orleans, LA; 3. Division of Pulmonary, Allergy, & Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL; 4. Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA

Corresponding author:
Jonathan D. Casey, MD
T-1210 MCN, 1161 21st Ave S., Nashville, TN 37232-2650
Fax: (615) 343-7448
Email: jonathan.d.casey@vanderbilt.edu

Authors contributions: Study concept and design: J.D.C., M.W.S, D.R.J., and T.W.R.; Acquisition of data: J.D.C, D.R.J., D.W.R, D.J.V., A.M.J., K.M.D., R.M.B., M.G.L., A.N.Z, S.G, W.S.S., and M.W.S.; Analysis and interpretation of data: J.D.C, and M.W.S.; Drafting of the manuscript: J.D.C, M.W.S.; Critical revision of the manuscript for important intellectual content: J.D.C, R.M.B., and M.W.S.; Statistical analysis: J.D.C. and M.W.S.; Study supervision: T.W.R.
Sources of Funding: J.D.C. was supported in part by the NIH (2T32HL087738-12). M.W.S. was supported in part by the NHLBI (HL087738-09 and K12HL133117). D.W.R

was supported in part by the NIH/NHLBI (T32HL105346-07). T.W.R. was supported in part by the NIH (R34HL105869). Data collection utilized the Research Electronic Data Capture (REDCap) tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH). The funding institutions had no role in (1) conception, design, or conduct of the study, (2) collection, management, analysis, interpretation, or presentation of the data, or (3) preparation, review, or approval of the manuscript.

Conflicts of Interest: All authors completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors declared no potential conflicts of interest with the current work. T.W.R. reported serving on an advisory board for Avisa Pharma, LLC, and as the Director of Medical Affairs for Cumberland Pharmaceuticals, Inc.

Key words for indexing: Endotracheal intubation, ventilation, hypoxemia

Subject Descriptor Number: 4.4 Clinical Trials in Critical Care Medicine

Manuscript Word Count (body only): 4100

Abstract Word Count: 256

Supplemental digital content is available for this article.

ABSTRACT:

Introduction: Hypoxemia is the most common complication during endotracheal intubation of critically ill adults, and it increases the risk of cardiac arrest and death. Manual ventilation between induction and intubation has been hypothesized to decrease the incidence of hypoxemia, but efficacy and safety data are lacking.

Methods and analysis: The Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation (PreVent) trial is a prospective, multi-center, non-blinded randomized clinical trial being conducted in seven intensive care units in the United States. A total of 400 critically ill adults undergoing endotracheal intubation will be randomized 1:1 to receive prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device or no prophylactic ventilation. The primary outcome is the lowest arterial oxygen saturation between induction and two minutes after successful endotracheal intubation, which will be analyzed as an unadjusted, intention-to-treat comparison of patients randomized to prophylactic ventilation versus patients randomized to no prophylactic ventilation. The secondary outcome is the incidence of severe hypoxemia, defined as any arterial oxygen saturation of less than 80% between induction and two minutes after endotracheal intubation. Enrollment began on February 2, 2017 and is expected to be complete in May 2018.

Ethics and dissemination:

The trial was approved by the institutional review boards or designees of all participating centers. The results will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

Trial Registration: The trial was registered with ClinicalTrials.gov (NCT03026322) on January 20, 2017, prior to the enrollment of the first patient on February 2, 2017.

ARTICLE SUMMARY

Strengths and limitations of this study

- This ongoing pragmatic trial will provide the first comparison of clinical outcomes with prophylactic ventilation versus no prophylactic ventilation during endotracheal intubation of critically ill adults
- Enrolling patients at multiple centers using broad inclusion criteria will enhance the generalizability of the findings.
- The nature of the study intervention does not allow blinding
- Despite being one of the largest randomized trials to examine endotracheal intubation of critically ill patients, statistical power will be inadequate to detect differences between study groups in uncommon outcomes (e.g., operator-reported aspiration).

INTRODUCTION

Endotracheal intubation is common in the care of critically ill patients and is frequently associated with complications [1–3]. Hypoxemia occurs in approximately 40% of intubations outside the operating room, and is associated with an increased risk for cardiac arrest and death [2,4–7].

Rapid sequence intubation is the nearly simultaneous administration of a sedative and neuromuscular blocking agent (paralytic) to facilitate endotracheal intubation. This technique is intended to maximize the chances of intubation on the first laryngoscopy attempt and minimize the risk of aspiration. Rapid sequence intubation has been shown to increase the incidence of successful intubation on the first laryngoscopy attempt and to decrease complications compared to intubation without neuromuscular blockade [8–10]. Regardless of the choice of induction agent and neuromuscular blocker, rapid sequence intubation involves an inherent delay between medication administration and onset of paralysis, at which time laryngoscopy is initiated. The relative benefits and risks of providing ventilation to patients during this interval are unknown. Some airway management texts and guidelines recommend that, for patients who are not hypoxemic, no ventilation be provided between induction and intubation, allowing the patient to remain hypopneic or apneic with the onset of sedation and neuromuscular blockade (Figure 1).[11–18] This approach prioritizes minimizing the potential risk of aspiration over any potential benefit of preventing the development of hypoxemia and hypercapnia. Other airway management texts and guidelines recommend the provision of manual ventilation between induction and intubation using a bag-valve-mask device for all patients, including those who are not hypoxemic (referred to hereafter as

"prophylactic ventilation") (Figure 2).[1,17,17,19–22] This approach prioritizes the potential benefit of preventing the development of hypoxemia and hypercapnia over the potential risk of aspiration. National and international surveys of anesthesiologists demonstrate that up to 50% of anesthesia practitioners report routinely performing prophylactic ventilation between induction and intubation during out-of-OR intubations.[23,24] The most recent published guidelines on intubation of critically ill adults recognizes the arguments for and against prophylactic ventilation without making any recommendation as to whether or not it should be used.[25]

Hundreds of thousands of critically ill adults require endotracheal intubation each year in the United States alone, but despite the frequency of this procedure, there are currently no high-quality data available to help providers understand the potential benefits and risks of providing prophylactic ventilation between induction and intubation [26]. To address this knowledge gap, we designed a multicenter, randomized trial comparing prophylactic ventilation to no prophylactic ventilation during endotracheal intubation of critically ill adults. We hypothesize that, compared to no prophylactic ventilation, prophylactic ventilation will significantly increase the lowest arterial oxygen saturation between induction and two minutes after endotracheal intubation.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Figure 3; SPIRIT checklist in online supplement, section 1). [27]

Study Design

The Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation (PreVent) trial is a multi-center, parallel-group, un-blinded, pragmatic randomized trial being conducted in seven intensive care units at five medical centers across the United States. The trial compares prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device to no prophylactic ventilation during endotracheal intubation of critically ill adults. Enrollment began on February 2, 2017 and is expected to be complete in May 2018. The primary outcome is lowest arterial oxygen saturation between induction and two minutes after endotracheal intubation. The trial was registered with ClinicalTrials.gov prior to initiation of patient enrollment (ClinicalTrials.gov identifiers: NCT03026322). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial.

Patient and Public Involvement

Patients and the public were not involved in identifying the research question or the design of the study. We plan to disseminate the results of the study to the public at the completion of the trial.

Study sites

The trial is being conducted at seven academic intensive care units across the United States: a 35-bed medical ICU at Vanderbilt University Medical Center in Nashville, Tennessee; a 38-bed medical, cardiac, and neurological ICU at University Medical Center in New Orleans, Louisiana; a 33-bed medical ICU at Ochsner Medical Center in New Orleans, Louisiana; a 25-bed medical ICU at University of Alabama at Birmingham Medical Center in Birmingham, Alabama; and a 17-bed medical ICU, a 30-bed neurological ICU, and 24-bed trauma ICU at University of Washington Harborview Medical Center in Seattle, Washington.

Population

The inclusion criteria for the trial are:

1. adult patient (age ≥ 18 years);
2. located in a participating ICU; for whom
3. treating clinicians have determined endotracheal intubation is required;
4. planned procedural approach includes administration of an induction agent (with or without neuromuscular blockade); and
5. first operator who routinely performs endotracheal intubation in the participating ICU.

The exclusion criteria for the trial are:

1. pregnant women;
2. prisoners;

3. patients for whom the treating clinicians feel the urgency of the intubation precludes safe performance of study procedures; and
4. patients for whom a treating clinician feels a specific approach to ventilation between induction and intubation is required.

Patients are not excluded based on oxygen saturation at enrollment. A patient flow-chart diagram describing the number of patients screened for the trial, the number excluded, and the reasons for exclusion, will be included in the manuscript reporting the results of the trial.

Randomization and Treatment Allocation

Enrolled patients are randomized in a 1:1 ratio to prophylactic ventilation or no prophylactic ventilation. The allocation sequence was generated by study personnel at the coordinating center using computerized randomization in permuted blocks, stratified by study ICU. Study group assignments were placed in sequentially numbered opaque envelopes and distributed to the study ICUs. Group assignment remains concealed from local study personnel and treating clinicians until the determination has been made that a patient (1) requires endotracheal intubation, (2) meets all inclusion criteria, and (3) meets no exclusion criteria – at which point the enveloped is opened. After enrollment and randomization, patients, treating clinicians, and study personnel at the local site are not blinded to study group assignment.

Study Interventions

Definitions

Ventilation between induction and endotracheal intubation refers to the delivery of positive pressure breaths using a non-invasive ventilator or a bag-valve-mask device. Prophylactic ventilation describes ventilation administered to a patient without hypoxemia to prevent the development of hypoxemia. Separately, ventilation may represent treatment of hypoxemia for patients who are experiencing hypoxemia at the initiation of ventilation. The focus of this trial is on the administration of manual ventilation with a bag-valve-mask device to prevent the development of hypoxemia. Treatment of hypoxemia with manual ventilation is not considered prophylactic ventilation and is allowed at any time in either study group. Administration of ventilation with a non-invasive ventilator between induction and laryngoscopy is prohibited in both study groups because it represents a source of confounding with regard to the provision of prophylactic ventilation. Pre-oxygenation prior to induction is allowed in either group with any pre-oxygenation modality, including non-invasive ventilation.

Prophylactic Ventilation

For patients assigned to the prophylactic ventilation group, manual ventilation is provided using a bag-valve-mask device beginning at induction and continuing until the initiation of laryngoscopy. If more than one attempt at laryngoscopy occurs, manual ventilation using a bag-valve-mask device may be reinstituted between laryngoscopy attempts. Manual ventilation may be discontinued at any point if felt by the treating clinicians to be necessary for patient safety.

Manual ventilation with a bag-valve-mask device is a routinely employed technique familiar to clinicians who perform endotracheal intubation in the ICU. In

keeping with the pragmatic nature of the trial, manual ventilation with a bag-valve-mask device is provided during the trial by the same treating clinicians who would perform the intervention outside of a research setting. Trainees responsible for airway management in participating units received an educational intervention prior to the beginning of enrollment reviewing best practices in manual ventilation using a bag-valve-mask device. This training emphasized proper mask placement, airway patency maneuvers, positive end-expiratory pressure (PEEP), oxygen flow rates, and ideal ventilation rates and volumes. In addition, the group assignment sheet for the prophylactic ventilation group includes reminders of best practices for manual ventilation using a bag-valve-mask device, including instructions to use: oxygen flow rates of at least 15 liters per minute; a PEEP valve set to 5-10 cm of water; an oral airway; a 2-handed mask seal performed by the intubating clinician with a head-tilt-chin-lift (with a stock photograph demonstrating proper technique); and ventilation at 10 breaths per minute until laryngoscopy. Details of patients' receipt of manual ventilation between induction and intubation are prospectively recorded. Failure to administer manual ventilation with a bag-valve-mask device beginning at induction is documented as a protocol violation.

No Prophylactic Ventilation

Patients assigned to the no prophylactic ventilation group do not receive prophylactic ventilation between induction and intubation. Manual ventilation is allowed as treatment (1) for hypoxemia (oxygen saturation < 90%) or (2) following a failed laryngoscopy attempt. In addition, manual ventilation may be initiated at any point if felt by the treating clinicians to be necessary for the safe treatment of the patient. Details of patients' receipt of ventilation between induction and endotracheal intubation are

prospectively recorded. Administration of ventilation using a bag-valve-mask device before the first attempt at laryngoscopy in a patient who does not experience hypoxemia (oxygen saturation < 90%) is documented as a protocol violation. The group assignment sheet for the no prophylactic ventilation group includes reminders that apneic oxygenation is allowed, that non-invasive ventilation should be removed at induction, and that bag-valve-mask ventilation is allowed for oxygen saturation < 90%.

Co-interventions

Study group assignment determines only the approach to prophylactic ventilation between induction and endotracheal intubation. Treating clinicians determine the need for intubation, approach to pre-oxygenation, patient positioning, choice and timing of medications for induction and neuromuscular blockade, choice of laryngoscope type and size, use of cricoid pressure, and use of additional airway management equipment.

Data Collection

A trained, independent observer, not affiliated with the performance of the procedure collects data for key peri-procedural outcomes, including oxygen saturation and systolic blood pressure at induction, lowest arterial oxygen saturation and systolic blood pressure between induction and 2 minutes following intubation, vasopressor administration, and time to intubation. The accuracy of data collection by the independent observers is confirmed by concurrent assessment of the same outcomes by the primary investigators for a convenience sample of approximately 10% of study intubations.

Cormack-Lehane grade of glottic view [28], subjective difficulty of intubation, and airway complications during the procedure are reported by the operator. Operators self-report their prior intubating experience at the time of each study intubation.

Study personnel collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes from the medical record. The following variables are collected:

Baseline: Age, gender, height, weight, body mass index, race, Acute Physiology and Chronic Health Evaluation (APACHE II score), active medical problems at the time of intubation, active comorbidities complicating intubation, comorbidities known to increase risk of aspiration (history of gastroesophageal reflux, narcotic use, functional or mechanical gastrointestinal obstruction, previous esophageal surgery, head injury, active emesis, or active upper gastrointestinal bleeding), indication for intubation, reintubation status, preoxygenation technique, operator experience, non-invasive ventilator use, vasopressor use, arterial blood gas results, and the highest fraction of inspired oxygen delivered (FiO2), lowest systolic blood pressure observed, and lowest oxygen saturation observed in the six hours preceding intubation.

Peri-procedural: Pre-procedural fluid and vasopressors. Date and time of sedative administration, saturation at time of sedative administration, type and dose of sedative, type and dose of neuromuscular blocker, use of manual ventilation starting at the time of induction, any use of ventilation during the intubation, indication for ventilation (study assignment, oxygen saturation less than 90%, following a failed attempt, other), use of oral or nasal airway, use of

cricoid pressure, laryngoscope type and size, total number of attempts, airway grade, airway difficulty, use of rescue device(s), need for additional operators, date and time of first laryngoscopy attempt, date and time of successful intubation, mechanical complications (esophageal intubation, airway trauma), bradycardia, and the presence of aspiration between induction and intubation (reported by operator).

0-48 hours: All chest imaging obtained within the first 48 hours after intubation, post intubation shock or cardiac arrest, Highest and lowest SaO2, FiO2, PEEP, and systolic blood pressure in the 1, 6, and 24 hours after intubation.

In-Hospital Outcomes: Ventilator-free days, ICU-free days, and in-hospital mortality. Definitions for Ventilator-free days and ICU-free days can be found in the online supplement, sections 2 and 3.

Primary Outcome

The primary outcome is the lowest arterial oxygen saturation measured by continuous pulse oximetry (SpO2) between induction and 2 minutes after endotracheal intubation ("lowest arterial oxygen saturation") as documented by the independent observer.

Secondary Outcome

The single, pre-specified, secondary outcome is the incidence of severe hypoxemia, defined as any oxygen saturation less than 80% between induction and 2 minutes after endotracheal intubation. The optimal outcome for clinical trials attempting

to improve oxygenation during endotracheal intubation of critically ill adults is unknown. In addition to the primary outcome of lowest arterial oxygen saturation as a continuous variable, some experts have recommended examination of the endpoint of "severe hypoxemia" as a dichotomous outcome. We therefore highlight the incidence of oxygen saturation less than 80% as our pre-specified approach to analysis of lowest oxygen saturation as a dichotomous outcome. All additional outcomes are exploratory and will be considered hypothesis generating.

Main Safety Outcomes

The main safety outcomes will be the lowest SpO2, highest FiO2, and highest PEEP in the time period of 6 to 24 hours post-intubation. The outcomes of SpO2, FiO2, and PEEP are selected to capture objective clinical manifestations of peri-procedural aspiration. The time point of 6 to 24 hours post-intubation is chosen to account for the practice, at some centers, of initiating patients at 100% FiO2 and low PEEP immediately after intubation, and subsequently titrating FiO2 and PEEP over several hours to achieve the target SpO2.

Exploratory Procedural Outcomes

- Cormack-Lehane grade of glottic view
- Operator-assessed difficulty of intubation
- Incidence of successful intubation on the first laryngoscopy attempt
- Number of laryngoscopy attempts
- Time from induction to successful intubation

- Incidence of esophageal intubation
- Need for additional airway equipment or a second operator
- Incidence of lowest oxygen saturation less than 90%
- Change in oxygen saturation from induction to lowest oxygen saturation
- Incidence of desaturation, defined as a change in oxygen saturation of more than 3% from induction to 2 minutes after endotracheal intubation

Exploratory Safety Outcomes

- Operator-reported aspiration during the procedure, defined as visualization of oropharyngeal or gastric contents in the pharynx, larynx, or trachea between induction and completion of airway management
- New infiltrate on chest x-ray in the 48 hours following intubation, as determined by an independent reviewer; details in online supplement, section 4
- New pneumothorax within 24 hours of intubation, as determined by an independent reviewer; details in online supplement, section 4
- New pneumomediastinum within 24 hours of intubation, as determined by an independent reviewer; details in online supplement, section 4
- Lowest systolic blood between induction and two minutes after endotracheal intubation
- New systolic blood pressure < 65 mmHg or new vasopressor administration between induction and 2 minutes after endotracheal intubation

- Cardiac arrest within one hour of intubation
- Death within one hour of intubation
- Lowest SpO2, highest FiO2, and highest PEEP from 0-1 and 1-6 hours
- The composite of operator-reported pulmonary aspiration, new chest x-ray infiltrate, OR lowest oxygen saturation < 80% between induction and completion of endotracheal intubation

Exploratory Clinical Outcomes

- Ventilator-free days to 28 days
- ICU-free days to 28 days
- In-hospital mortality

Sample Size Estimation

Full details of the initial sample size calculation can be found in the online supplement, section 5. In short, using PS version 3.1.2[29] and assuming a standard deviation of 14% in lowest oxygen saturation (the primary outcome) and less than 5% missing data, we calculated that enrolling 350 patients would provide 90% power to detect a difference of 5% between groups in lowest oxygen saturation at a two-sided alpha of 0.05. The trial protocol and DSMB charter specified that the DSMB would recommend sample size re-estimation at the interim analysis if the standard deviation for lowest oxygen saturation in the control arm was larger than 14%, in order to prevent the final study from being underpowered to detect the planned difference between groups in lowest oxygen saturation. At the interim analysis, the observed standard

deviation for lowest oxygen saturation in the control arm was 15%. To maintain 90% statistical power to detect a 5% difference between groups in lowest oxygen saturation, the DMSB recommended increasing the sample size to 400 patients. Additional details of the sample size re-estimation can be found in the online supplement, section 6.

Data and Safety Monitoring Board and Interim Analysis

An independent DSMB was appointed to oversee the conduct of the trial and review one interim analysis (DSMB charter available in the online supplement, section 7). The DSMB was comprised of two academic intensivists experienced in the conduct of clinical trials. The DSMB conducted a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 175 patients. The stopping boundary for efficacy was specified as a P value of 0.001 or less for the difference between groups in the primary outcome. Use of a conservative Haybittle-Peto boundary ($P < 0.001$) allows the final analysis to be performed using an unchanged level of significance ($P = 0.05$). The primary determination of safety was based on the highest FiO2 and highest PEEP between 6 and 24 hours after intubation. If (1) the P value for the difference between study groups in both of these physiologic variables was less than 0.001, (2) the difference between groups in both physiologic variables was concordant in direction with the point estimate for in-hospital mortality, and (3) the P value for the difference between study groups in in-hospital mortality was less than 0.1, it was recommended that the study be stopped early for safety.

The DSMB was also provided with data in each group on the rates of operator-reported aspiration and new infiltrates, pneumothorax, or pneumomediastinum on chest

imaging. Although no pre-specified rules dictated stopping based on operator-reported aspiration or imaging findings without associated changes in physiologic or clinical outcomes, the DSMB reserved the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

At the time of submission of this manuscript, the DSMB has completed the sole planned interim analysis following the enrollment of the first 175 patients. The DSMB has recommended continuing the trial to completion with the only change being to increase the sample size to 400 patients, as described above.

Additional details on data storage, patient privacy, and the pre-specified process for protocol changes can be found in the online supplement, sections 8 and 9.

Statistical Analysis Principles

All analyses will be performed using Stata version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) and confirmed with SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) or R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank-sum test for continuous variables, and the chi-square test or Fishers exact test for categorical variables. Agreement between continuous variables measured independently by two observers

will be examined using Spearman rank correlation coefficient and Bland-Altman analysis. A two-sided P value < 0.05 will indicate statistical significance.

Primary Analysis

The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to prophylactic ventilation versus patients randomized to no prophylactic ventilation with regard to the primary outcome of lowest arterial oxygen saturation between induction and 2 minutes after endotracheal intubation. The difference between the two study groups will be compared using the Mann-Whitney rank-sum test.

Secondary Analyses

We will conduct the following pre-specified secondary analyses:

1. **Secondary and Exploratory Outcomes**. We will perform unadjusted, intention-to-treat analyses comparing patients in the prophylactic ventilation group to the no prophylactic ventilation group with regard to each of the pre-specified secondary and exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney rank-sum test and categorical variables with the chi-square test.
2. **Per-Protocol Analysis**. We will perform a per-protocol analysis comparing patients who received prophylactic manual ventilation beginning at induction (regardless of group assignment) to patients who did not receive prophylactic manual ventilation beginning at induction

(regardless of group assignment). Patients who were hypoxemic at induction and received manual ventilation as treatment for hypoxemia will be analyzed in the group to which they were assigned.

3. **Effect Modification (Subgroup Analyses)**. We will examine whether pre-specified baseline variables modify the effect of study group on the primary outcome. We will evaluate for effect modification by fitting a linear regression model for the primary outcome of lowest arterial oxygen saturation. Independent variables will include study group assignment, the potential effect modifier variable of interest, and the interaction between the two (e.g., study group*oxygen saturation at induction). Significance will be determined by the *P* value for the interaction term, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. Subgroups derived from categorical variables will be displayed as a forest plot. Continuous variables will be analyzed using restricted cubic splines with 3-5 knots and preferentially displayed as continuous variables using a locally weighted regression or partial effects plots. If the presentation of data requires it, dichotomization of continuous variables for inclusion in a forest plot will be performed. Pre-specified subgroups that may modify the effect of prophylactic ventilation include:

    1. Predicted lowest arterial oxygen saturation (“risk of hypoxemia”) as calculated by a pre-specified multivariable model (continuous variable)

2. Oxygen saturation at induction (continuous variable)
3. Highest FiO2 received in the 6 hours prior to intubation (continuous variable)
4. Receipt of non-invasive ventilation in the 6 hours prior to intubation (yes / no)
5. Indication for intubation (hypoxemic respiratory failure, not hypoxemic respiratory failure)
6. Neuromuscular blocking agent (depolarizing, non-depolarizing, none)
7. APACHE II score at enrollment (continuous variable)
8. Body mass index (continuous variable)
9. Operator's prior number of endotracheal intubations (continuous variable)
10. Operator training (pulmonary/critical care medicine, anesthesia)
11. Type of laryngoscope (direct laryngoscope, video laryngoscope)

4. **Multivariable Modeling to Account for Confounding**. To account for relevant confounders, we will develop a linear regression model with the primary outcome as the dependent variable and study group and relevant confounders included as independent variables (age, APACHE II score at enrollment, oxygen saturation at induction, highest FiO2 delivered in the 6 hours prior to intubation, and receipt of non-invasive ventilation in the 6 hours prior to intubation)

Missing Data

Based on prior trials in similar settings, we anticipate less than 5% missing data for the primary outcome. For the primary analysis, missing data will not be imputed. As sensitivity analyses, the primary analysis will be repeated with missing data imputed by (1) assigning a value of "0" to data missing for the lowest arterial oxygen saturation in the prophylactic ventilation group and "100" to data missing for the lowest arterial oxygen saturation in the no prophylactic ventilation group, and (2) assigning a value of "100" to data missing for the lowest arterial oxygen saturation in the prophylactic ventilation group and a value of "0" to data missing from the no prophylactic ventilation group.

Corrections for multiple testing

We have pre-specified a single primary analysis of a single primary outcome. All additional analyses will be considered hypothesis generating, and no corrections for multiple comparisons will be performed.

Trial Status

PreVent is an ongoing pragmatic trial comparing prophylactic ventilation using a bag-valve-mask to no prophylactic ventilation during endotracheal intubation of critically ill adults. Patient enrollment began on February 2, 2017, and we estimate that enrollment will end in May 2018.

Ethics and dissemination:

Consent

Prophylactic manual ventilation between induction and endotracheal intubation using a bag-valve-mask device and no prophylactic ventilation are each recommended approaches to endotracheal intubation of acutely ill adults [13,25]. Currently, no randomized trials or evidence-based guidelines support the choice of one approach over the other. Both approaches are used intermittently in current care in the study ICUs. Moreover, the current study specifically excludes patients for whom treating clinicians feel that the provision of prophylactic ventilation is either required or contraindicated.

The current study is felt by the investigators to represent minimal risk because the interventions studied (1) are used in current clinical care in the participating ICUs, (2) are interventions to which patients would be exposed even if not participating in research, (3) have no prior data to suggest the superiority of one approach over the other, and (4) are equivalent options from the perspective of the treating clinicians performing the procedure (otherwise the patient is excluded from the trial). Additionally, endotracheal intubation of critically ill adults is frequently a time-sensitive procedure for which obtaining informed consent is impractical. Given the minimal risk and impracticability of obtaining informed consent, a waiver of informed consent was requested from the Vanderbilt University Institutional Review Board.

IRB Approval

The trial was approved by the Institutional Review Board (IRB) of Vanderbilt University Medical Center (the coordinating center) with waiver of informed consent (IRB 161962). All participating centers obtained local IRB approval (Louisiana State

University Health Sciences Center IRB Number 00000177 and Ochsner Clinic Foundation IRB Number 2017.119.B) or deferred to Vanderbilt University Medical Center through a central IRB process (University of Alabama and University of Washington).

Publication

The results of the trial will be submitted for publication in a peer-reviewed journal and presented at one or more scientific conferences.

CONCLUSION

We describe, before the conclusion of enrollment or data un-blinding, our approach to analyzing the data from a pragmatic multicenter randomized trial comparing prophylactic ventilation between induction and intubation using a bag-valve-mask to no prophylactic ventilation (PreVent trial). We anticipate that this pre-specified framework will enhance the utility of the reported result and allow readers to better judge the impact.

REFERENCES

1 Schwartz DE, Matthay MA, Cohen NH. Death and Other Complications of Emergency Airway Management in Critically Ill Adults A Prospective Investigation of 297 Tracheal Intubations. *J Am Soc Anesthesiol* 1995;**82**:367–76.

2 Simpson GD, Ross MJ, McKeown DW, *et al.* Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;**108**:792–9. doi:10.1093/bja/aer504

3 Leibowitz AB. Tracheal intubation in the intensive care unit: Extremely hazardous even in the best of hands*: *Crit Care Med* 2006;**34**:2497–8. doi:10.1097/01.CCM.0000235993.47514.8F

4 Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: A justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth* 2004;**16**:508–16. doi:10.1016/j.jclinane.2004.01.007

5 Martin LD, Mhyre JM, Shanks AM, *et al.* 3,423 Emergency Tracheal Intubations at a University Hospital: Airway Outcomes and Complications. *Anesthesiology* 2011;**114**:42–8. doi:10.1097/ALN.0b013e318201c415

6 Griesdale DEG, Bosma TL, Kurth T, *et al.* Complications of endotracheal intubation in the critically ill. *Intensive Care Med* 2008;**34**:1835–42. doi:10.1007/s00134-008-1205-6

7 Semler MW, Janz DR, Lentz RJ, *et al.* Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med* 2015;**193**:273–80. doi:10.1164/rccm.201507-1294OC

8 Brown III CA, Bair AE, Pallin DJ, *et al.* Techniques, Success, and Adverse Events of Emergency Department Adult Intubations. *Ann Emerg Med* 2015;**65**:363-370.e1. doi:10.1016/j.annemergmed.2014.10.036

9 Li J, Murphy-Lavoie H, Bugas C, *et al.* Complications of emergency intubation with and without paralysis. *Am J Emerg Med* 1999;**17**:141–3. doi:10.1016/S0735-6757(99)90046-3

10 Jaber S, Amraoui J, Lefrant J-Y, *et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: A prospective, multiple-center study*: *Crit Care Med* 2006;**34**:2355–61. doi:10.1097/01.CCM.0000233879.58720.87

11 Wylie WD. The Use of Muscle Relaxants at the Induction of Anaesthesia of Patients with a Full Stomach. *Br J Anaesth* 1963;**35**:168–73. doi:10.1093/bja/35.3.168

12 Salem MR. Anesthetic management of patients with “a full stomach”. A critical review. *Anesth Analg* 1970;**49**:47–55.

13 Walls RM. Rapid Sequence Intubation. In: *Manual of Emergency Airway Management*. Philadelphia: : Lippincott Williams & Wilkins, a Wolters Kluwer business 2012. 221–31.

14 Natanson C, Shelhamer JH, Parrillo JE. Intubation of the Trachea in the Critical Care Setting. *JAMA* 1985;**253**:1160–5. doi:10.1001/jama.1985.03350320084023

15 Caputo N, Azan B, Domingues R, *et al.* Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial). *Acad Emerg Med* 2017;**24**:1387–94. doi:10.1111/acem.13274

16 Stollings JL, Diedrich DA, Oyen LJ, *et al.* Rapid-Sequence Intubation: A Review of the Process and Considerations When Choosing Medications. *Ann Pharmacother* 2014;**48**:62–76. doi:10.1177/1060028013510488

17 El-Orbany M, Connolly LA. Rapid sequence induction and intubation: current controversy. *Anesth Analg* 2010;**110**:1318–25. doi:10.1213/ANE.0b013e3181d5ae47

18 Stept WJ, Safar P. Rapid induction-intubation for prevention of gastric-content aspiration. *Anesth Analg* 1970;**49**:633–6.

19 Nagelhout JJ. AANA journal course. Update for nurse anesthetists. Aspiration prophylaxis: is it time for changes in our practice? *AANA J* 2003;**71**:299–303.

20 Herriger A, Frascarolo P, Spahn DR, *et al.* The effect of positive airway pressure during pre-oxygenation and induction of anaesthesia upon duration of non-hypoxic apnoea. *Anaesthesia* 2004;**59**:243–7. doi:10.1111/j.1365-2044.2004.03615.x

21 Frerk C, Mitchell VS, McNarry AF, *et al.* Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. *BJA Br J Anaesth* 2015;**115**:827–48. doi:10.1093/bja/aev371

22 Myatra SN, Ahmed SM, Kundra P, *et al.* The All India Difficult Airway Association 2016 guidelines for tracheal intubation in the Intensive Care Unit. *Indian J Anaesth* 2016;**60**:922–30. doi:10.4103/0019-5049.195485

23 Ehrenfeld JM, Cassedy EA, Forbes VE, *et al.* Modified Rapid Sequence Induction and Intubation: A Survey of United States Current Practice. *Anesth Analg* 2012;**115**:95–101. doi:10.1213/ANE.0b013e31822dac35

24 Schlesinger S, Blanchfield D. Modified rapid-sequence induction of anesthesia: a survey of current clinical practice. *AANA J* 2001;**69**:291–8.

25 Higgs A, McGrath BA, Goddard C, *et al.* Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* doi:10.1016/j.bja.2017.10.021

26 Pfuntner A, Wier LM, Stocks C. Most Frequent Procedures Performed in U.S. Hospitals, 2011: Statistical Brief #165. In: *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Rockville (MD): : Agency for Healthcare Research and Quality (US) 2013. http://www.ncbi.nlm.nih.gov/books/NBK174682/ (accessed 4 Jun 2018).

27 SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/23303884 (accessed 8 Jan 2018).

28 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;**39**:1105–11. doi:10.1111/j.1365-2044.1984.tb08932.x

29 Dupont WD, Plummer WD. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990;**11**:116–28.

FIGURES

Figure 1.

Phases of rapid sequence intubation without prophylactic manual ventilation.
"NMB" is Neuromuscular blockade. "RSI" is rapid sequence intubation

Figure 2.

Phases of rapid sequence intubation with prophylactic manual ventilation.
"NMB" is Neuromuscular blockade. "RSI" is rapid sequence intubation

Figure 3.

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments.
Baseline variables obtained from electronic medical record include: demographic characteristics, indication for intubation, history of pulmonary disease, severity of illness at enrollment, risk factors for aspiration, non-invasive ventilator use, and highest FIO2 in the 6 hours prior to intubation. Peri-procedural variables, including oxygen saturation at induction, lowest arterial oxygen saturation between induction and 2 minutes following endotracheal intubation, and time to intubation will be collected by a trained, independent observer, not affiliated with the performance of the procedure. Clinical outcomes include: vital status, number of ventilator-free days to 28 days, and number of ICU-free days to 28 days. ICU is intensive care unit; ETI is endotracheal intubation.

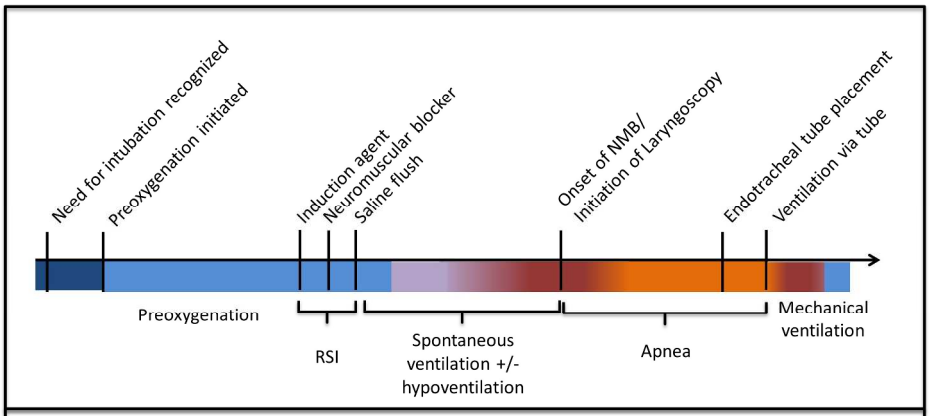

Figure 1: Phases of "Classic" Rapid Sequence Intubation

Figure 1

254x190mm (300 x 300 DPI)

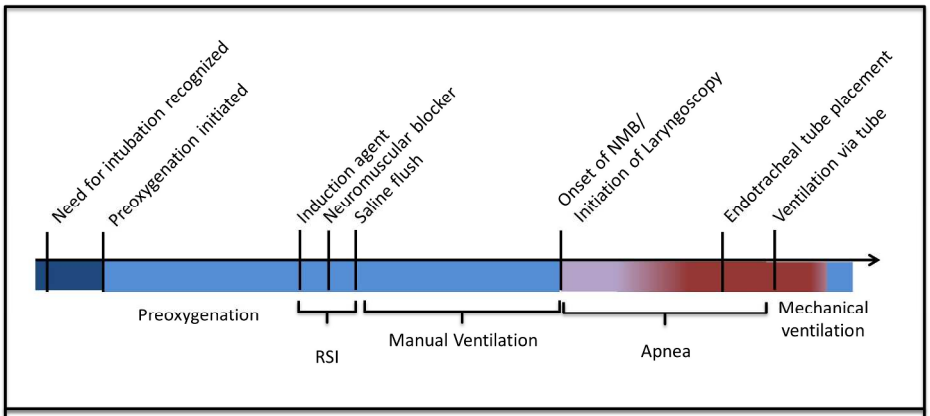

Figure 2: Phases of Modified Rapid Sequence Intubation

Figure 2

254x190mm (300 x 300 DPI)

Figure 3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments.

	STUDY PERIOD						
	Enrolment	Allocation	On-Study				Follow Up
TIMEPOINT	*Decision to perform ETI*	Prior to Induction	*Induction & NMB*	*ETI*	*2 min post-ETI*	48 hrs post-ETI	*Discharge or 30 days after enrollment*
ENROLMENT:	X						
Eligibility screen	X						
Allocation		X					
INTERVENTIONS:							
Prophylactic Ventilation			⟷	⟷			
Screening for contraindications	X	X	X	X			
No Prophylactic Ventilation			⟷	⟷			
Screening for contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-procedural variables		X	X	X	X		
Clinical Outcomes						X	X

Figure 3

215x279mm (300 x 300 DPI)

ONLINE SUPPLEMENT TO:

Preventing hypoxemia with manual ventilation during endotracheal intubation: protocol and statistical analysis plan for a multi-center randomized trial

Jonathan D. Casey, David R. Janz, MD, Derek W. Russell, Derek J. Vonderhaar, Aaron M. Joffe, Kevin M. Dischert, Ryan M. Brown, Michael G. Lester, Aline N. Zouk, Swati Gulati, William S. Stigler, Todd W. Rice, Matthew W. Semler for the PreVent Investigators and the Pragmatic Critical Care Research Group.

Table of Contents

1. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	1-2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1-2

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-2
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-2, 8, 18-19
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-13
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9-10

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-23
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	20-23
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20-23

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19, S10-S17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19, S10-S17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	S13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	S13-S14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24-25
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	S9
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	24-25
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	S9

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1-2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	1-2, 23
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	S9
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

2. Definition of Ventilator Free Days (VFDs)

Ventilator-free days are defined as the number of days on which the patient is alive and breathing without assistance between the patient's final receipt of assisted breathing within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

3. Definition of ICU-Free Days (ICUFDs)

ICU-free days are defined as the number of days on which the patient is alive and not in an ICU between the patient's final transfer out of the ICU within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, ICU-free days are 0. If a patient is in an ICU at day 28, ICU-free days are 0. Otherwise, ICU-free days are calculated as 28 minus the study day on which the patient was ultimately transferred out of the ICU. All data will be censored at the time of first hospital discharge or 28 days.

4. Adjudication of new infiltrate, pneumothorax, or pneumomediastinum

Exploratory safety outcomes include new infiltrate on chest x-ray in the 48 hours following intubation, new pneumothorax within 24 hours of intubation, and new pneumomediastinum within 24 hours of intubation. The presence of new infiltrate, new pneumothorax, or new pneumomediastinum are determined by independent review of chest imaging by two pulmonary and critical care medicine attending physicians at the coordinating center who are unaware of study group assignment. Each site provides the coordinating center the most recent chest x-ray prior to intubation and all chest x-rays obtained between intubation and 48 hours after intubation. Each film is de-identified and reviewed independently by two pulmonary and critical care medicine attending physicians who are unaware of study group assignment. The presence or absence of new infiltrate, new pneumothorax, or new pneumomediastinum is recorded using a standardized data collection sheet. If a pre-intubation chest x-ray is not available, any infiltrate, pneumothorax, or pneumomediastinum is considered to be new. Any assessments that are discordant between the two independent reviewers are resolved by independent, blinded review by a third pulmonary and critical care medicine physician.

5. Initial Sample Size Calculation

The initial sample size calculation was made using data from previous prospective trials enrolling a similar population of patients in similar ICUs. These trials demonstrated a standard deviation of 14% in the primary outcome of lowest arterial oxygen saturation.[1] The difference between groups in lowest arterial oxygen saturation felt to be clinically meaningful in prior trials was 5%.[2–4] Using PS version 3.1.2 with the above assumptions and a two-sided alpha level of 0.05, we calculated that achieving a statistical power of 90% would require enrollment of 332 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 350 patients was planned.

6. Sample Size Re-estimation

The trial protocol and DSMB charter specified that the DSMB would recommend sample size re-estimation at the interim analysis if the standard deviation for lowest oxygen saturation in the control arm was larger than 14%, in order to prevent the final study from being underpowered to detect the planned difference between groups in lowest oxygen saturation. At the interim analysis, the observed standard deviation for lowest oxygen saturation in the control arm was 15%. Using nQuery Advisor® version 7.0, we calculated that maintaining a statistical power of 90% to show a difference of 5% in lowest oxygen saturation with a standard deviation of 15% and a two-sided alpha level of 0.05 would require enrollment of 380 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 400 patients would be required. Based on these calculations, the DMSB recommended increasing the final planned sample size to 400 patients.

To understand the ability of the updated sample size to inform the assessment of the safety of the intervention, we conducted exploratory sample size calculations for the safety outcomes. The main safety outcomes are lowest oxygen saturation, highest fraction of inspired oxygen (FiO2), and highest positive end-expiratory pressure (PEEP) from 6 to 24 hours after intubation between the two study groups. In the 24 hours following intubation in a prior trial in a similar population, the standard deviation in lowest oxygen saturation was 11%, the standard deviation in highest FiO2 was 0.33, and the standard deviation in highest PEEP was 3.3 cmH_2O.[28] By enrolling 400 patients, we estimated that we would have 80% statistical power at an alpha of 0.05 to detect a 3.1% difference between groups in the lowest oxygen saturation in the 24

hours after intubation, a 0.09 difference in the highest FiO2, and a 0.9 cmH_2O difference in highest PEEP.

The exploratory safety outcomes are less common clinical events than the primary outcome and the main safety outcomes. Operator-reported aspiration has occurred in prior trials at an incidence of 1.0-6.0%. Therefore, enrollment of 400 patients would provide 80% statistical power at an alpha level of 0.05 to detect an absolute difference in the incidence of aspiration between groups of 6.0-10.5%. New infiltrate on chest imaging following intubation has been reported in prior studies to occur with an incidence of 4-8%.[1,29] Enrollment of 400 patients would provide 80% power at an alpha level of 0.05 to detect an absolute difference between groups of 8.1-9.9%, respectively.

7. Data and Safety Monitoring Board Charter

DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for

"Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial"

Jonathan D. Casey, MD

David R. Janz, MD, MSc

Todd W. Rice, MD, MSc

Matthew W. Semler MD, MSc

Confidential Information

The information contained within this Charter is confidential and intended for the use of the DSMB

_____

DSMB Member Printed Name

_____ _____

DSMB Member Signature Date

Charter, Data and Safety Monitoring Board for

Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

January 2017

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the sponsor of this trial, Matthew W Semler, MD, MSc and is required to provide recommendations about starting, continuing, and stopping the trial. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Performance of individual centers
- Participant safety
- Notification of and referral for adverse events

3. Organization and Interactions

Communication with DSMB members will be primarily through Dr. Semler. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A. The DSMB consists of two physicians experienced in critical care, the conduct of clinical trials including data and safety monitoring, and have formal training to conduct statistical analyses necessary for the planned interim analysis. Dr. Semler or his designee will serve as the Executive Secretary (ES) and be responsible for keeping the minutes of the open sessions. The Chair of the DSMB will be responsible for recording the minutes of the closed sessions and for the timely transmission of the final DSMB recommendations to Dr. Semler. Dr. Semler will be responsible for the timely notification of investigators of all DSMB recommendations.

5. Scheduling, Timing, Content, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter and the study protocol, including the Data Safety Monitoring Plan. Dr. Semler or his designee can conduct this meeting with individual DSMB members or as a group. Enrollment in the study cannot begin until Dr. Semler has accepted the DSMB's recommendation for approval and IRB approval has been obtained. All DSMB members must sign and return the charter to Dr. Semler or his designee to indicate their approval.

Conference calls are to be held approximately twice a year, with additional conference calls scheduled as needed. Conference calls will be scheduled by Dr. Semler or the ES in collaboration with the DSMB members.

The DSMB will review 30-day data after 175 subjects have been enrolled; enrollment will continue during DSMB review. The primary focus of this review will be efficacy and safety. All data will be supplied to the DSMB with blinded treatment groups; however, the DSMB will be able to request unblinding for any reason. All serious adverse events thought to be related to study procedures will be reported to the DSMB on an ongoing basis; the study will be stopped for a safety evaluation by the DSMB if they have any concerns based on either the interim data analysis or review of serious adverse events.

The agenda for DSMB meetings and calls will be drafted by Dr. Semler. Dr. Semler will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the ES two weeks before each call.

Before each teleconference the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last call. If a new conflict is reported, the Chair will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

It is expected that all DSMB members will attend every call and respond to electronic mail communications promptly. A quorum of this DSMB will be all two members.

6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, Dr. Semler will present information to the DSMB on behalf of the study investigators with time for discussion.

- During the **closed sessions**, the DSMB will discuss confidential and/or unblinded data from the study. Steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

- Initial summary: The ES is responsible for assuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations. Dr. Semler will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, Dr. Semler will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The ES is responsible for the accuracy and transmission of the formal DSMB minutes within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email.

8. Reports to the DSMB

For each meeting, Dr. Semler will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first meeting what data they wish to review and how it should be presented. Data requests can be modified at subsequent meetings.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the clinical endpoints and safety monitoring plans. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial.

10. Stopping Rules

At the meeting for the planned interim analysis (at least 30 days after enrollment of 175 patients), the DSMB will be provided the following blinded data in raw format:

1. Study group assignment of each patient (A vs B)
2. Lowest arterial oxygen saturation during the procedure
3. Lowest arterial oxygen saturation in the 24 hours following intubation
4. Highest fraction of inspired oxygen in the 24 hours following intubation

5. Highest positive end expiratory pressure in the 24 hours following intubation
6. Mortality
7. Ventilator-free days

At this interim analysis, the DSMB will be asked to perform 2 analyses using these data: a efficacy analysis and safety analysis as described below. At the completion of these analyses, the DSMB will notify Dr. Semler if the trial should be stopped for any of these three reasons or continued to completion. The DSMB will not make Dr. Semler or any of the investigators aware of the results of any of their analyses. At the interim analysis or at any other time where the DSMB is deciding if the trial should be stopped or continued, all of the members of the DSMB must agree that the trial should be stopped or continued.

11. Efficacy Stopping Rules

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, 30 days after enrollment of 175 patients. Enrollment will continue during this period. The **stopping boundary for efficacy** will be met if the *P* value for the difference between groups in the primary outcome is 0.001 or less. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of both interventions as a part of usual care, there will be **no stopping boundary for futility**.

12.Safety Stopping Rule

With regards to safety, the DSMB will be able to stop study accrual at any time if there is concern for safety. Other than these concerns, the DSMB will be asked to formally evaluate the safety of the trial at the interim analysis described above 30 days after enrollment of 175 patients. The primary determination of safety will be based on the highest fraction of inspired oxygen and highest positive end-expiratory pressure between 6 and 24 hours after intubation. The **safety stopping boundary** is as follows:

1. The *P* value for the difference between study groups in both of these physiologic variables is < 0.001, AND
2. The difference between groups in both physiologic variables is concordant in direction with the point estimate for in-hospital mortality, AND
3. The *P* value for the difference between study groups in in-hospital mortality is < 0.1

The DSMB will also be provided with blinded data on all outcomes collected by the trial to use in their review of trial safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, unblind the study assignments, or request modifications of the study protocol as required to protect patient safety. Finally, the DSMB will have the ability to monitor the standard deviation of the primary outcome in the

control group at the interim analysis and can ask that the study be re-powered if the standard deviation of the primary outcome is different from our original estimate of 14%. This standard deviation will be calculated by the investigators and given to the DSMB in a blinded fashion.

8. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

9. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.